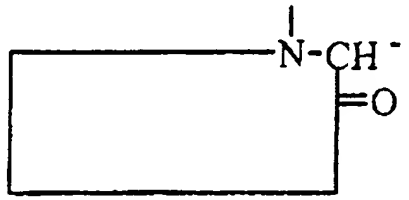
CLAIMS

1. A process for preparing a polyanion for use as an intermediate in the preparation of a cyclosporin derivative, said process comprising treating a cyclosporin with a hexamethyldisilazane metal salt.

2. The process according to claim 1, wherein said process occurs in the presence of a metal halide.

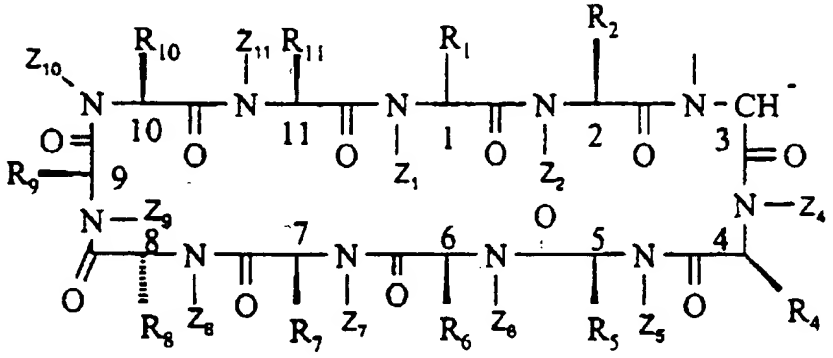
3. The process according to claim 1, in which said polyanion has the formula:



(I)

in which  is a cyclosporin in which one or more hydroxyl groups and optionally one or more non-methylated nitrogen atoms at the α position and optionally any other deprotonatable acidic group are optionally deprotonated or in the protected form.

4. The process according to claim 1, in which said polyanion has the formula:



(II)

in which:

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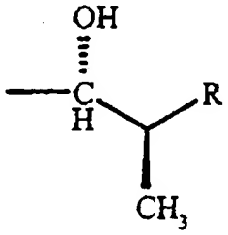
i) the radicals R_1, R_2, and R_4 to R_{11}, and Z_1, Z_2, and Z_4 to Z_{11} are defined as for cyclosporin A; or

ii) the radicals R_1, R_2, and R_4 to R_{11}, and Z_1, Z_2, and Z_4 to Z_{11} are defined as for cyclosporin A, with the exception of R_4 and Z_4, which are defined so as to have, at the 4-position, the amino acid 4'-hydroxy-methylleucine; or

iii) the radicals R_2 and R_5 to R_{11}, and Z_2 and Z_5 to Z_{11} are defined as for cyclosporin A; and

Z_1 is a methyl group and R_1 has the formula:



(IIIa)

in which R is a radical of formula $-CH_2-CH=CH-CH_2-R'$, in which R' is an alkylthio, aminoalkylthio, alkylaminoalkylthio, dialkylaminoalkylthio, pyrimidinylthio, thiazolylthio, N-alkylimidazolylthio, hydroxyalkylphenylthio, hydroxyalkylphenyloxy, nitrophenylamino, or 2-oxopyrimidin-1-yl radical; or

R is a radical of formula $-CH_2-S-Alk$ in which Alk, is an alkyl group; and

Z_4 and R_4 are radicals such that there is, at the 4-position, an amino acid methylleucine or 4'-hydroxy-methylleucine; or

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iv)

Z_1 and R_1 are radicals such that there is, at the 1-position, a substituted homothreonine of formula:

R_i-$CH_2CH(CH_3)$-CH(OH)-$CH(NHCH_3)$-COOH (IIIb)

in which R_i is *n*-propyl or propenyl; and

R_2 and Z_2 are radicals such that there is, at the 2-position, α-aminobutyric acid, valine, norvaline, or threonine; and

R_4 and Z_4 are radicals such that there is, at the 4-position, N-methyl-γ-hydroxyleucine or N-methyl-γ-acetyloxyleucine; and

R_5 and Z_5 are radicals such that there is, at the 5-position, valine; and

R_6, Z_6, R_9, Z_9, R_{10}, and Z_{10} are radicals such that there is, at the 6-, 9-, and 10-positions, N-methylleucine; and

Z_7 and R_7 are radicals such that there is, at the 7-position, alanine; and

Z_8 and R_8 are radicals such that there is, at the 8-position, D-alanine or D-serine; and

Z_{11} and R_{11} are radicals such that there is, at the 11-position, N-methylvaline; or

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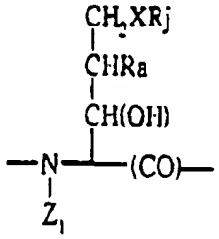
v) Z_1 and R_1 are radicals such that there is, at the 1-position, an methyl (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt) radical or a radical having the formula:



(IIIc)

in which R_j is a hydrogen atom or a lower alkyl group, a lower alkenyl, a lower haloalkyl, an aryl, a lower alkyloxy, an alkoxyC_{1-6}alkyl, a hydroxymethyl, a lower alkylthio, an alkylthioC_{1-6}alkyl, a C_{1-6} mercaptoalkyl, or a heteroaryl;

it being possible for the aryl and heteroaryl groups to be substituted with one or more functional groups chosen from: C_{1-6} alkyl; C_{1-6} alkanoyl; C_{1-6} haloalkyl; halo; cyano; C_{1-3} hydroxyalkyl; C_{1-6} alkyloxy; C_{1-6} alkyl-$S(O)_n$, where n = 0, 1, or 2; NR_bCOR_c, in which R_b and R_c independently are H or a C_{1-6} alkyl, $-NO_2$, $-NR_bR_c$, $-OR_b$, $-CONR_bR_c$, $-COR_b$, $-NR_bCONR_bR_c$, NR_bCOR_c, $-OCOR_b$, $-SCOR_b$, or $-OCH_2O-$; and

R_a is a lower alkyl; and

Z_1 is a lower alkyl, a lower phenylalkyl, or an aryl; and

X is S, SO, SO_2, O, or NR_b; and

Z_2 and R_2 are radicals such that there is, at the 2-position, the amino acid L-2-

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aminobutyric acid, Norvaline, L-Thr, or the same amino acid as at the 1-position; and

Z_4 and R_4 are radicals such that there is, at the 4-position, the amino acid N-methyl-L-leucine; and

Z_5 and R_5 are radicals such that there is, at the 5-position, the amino acid L-valine or norvaline; and

Z_6 and R_6 are radicals such that there is, at the 6-position, the amino acid N-methyl-L-leucine; and

Z_7 and R_7 are radicals such that there is, at the 7-position, the amino acid L-alanine, L-2-aminobutyric acid, or L-phenylalanine; and

Z_8 and R_8 are radicals such that there is, at the 8-position, the amino acid D-alanine or L-alanine; and

Z_9 and R_9 are radicals such that there is, at the 9-position, the amino acid N-methyl-L-leucine or N-methyl-L-valine; and

Z_{10} and R_{10} are radicals such that there is, at the 10-position, the amino acid N-methyl-L-leucine or L-leucine; and

Z_{11} and R_{11} are radicals such that there is, at the 11-position, the amino acid N-methyl-L-valine, L-valine, or L-2-aminobutyric acid; or

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vi) the radicals R_4 to R_{11} and Z_4 to Z_{11} are defined as for cyclosporin A; and

Z_1 and R_1 are radicals such that there is, at the 1-position, the amino acid MeBmt or dihydro-MeBmt; and

Z_2 and R_2 are radicals such that there is, at the 2-position, the amino acid α-aminobutyric acid, threonine, valine, or norvaline; or

vii) the radicals R_7 to R_{11} and Z_7 to Z_{11} are defined as for cyclosporin A; and

Z_1 and R_1 are radicals such that there is, at the 1-position, the amino acid MeBmt, dihydro-MeBmt, or 8'-hydroxy-MeBmt; and

Z_2 and R_2 are radicals such that there is, at the 2-position, the amino acid α-aminobutyric acid, valine, threonine, norvaline, or MeOThr; and

Z_4 and R_4 are radicals such that there is, at the 4-position, the amino acid methylleucine, γ-hydroxy-MeLeu, MeIle, MeVal, MeThr, MeAla, MeaIle, or MeaThr; and

Z_5 and R_5 are radicals such that there is, at the 5-position, the amino acid valine, Leu, MeVal, or methylleucine; and

Z_6 and R_6 are radicals such that there is, at the 6-position, the amino acid methylleucine, γ-hydroxy-MeLeu, or MeAla;

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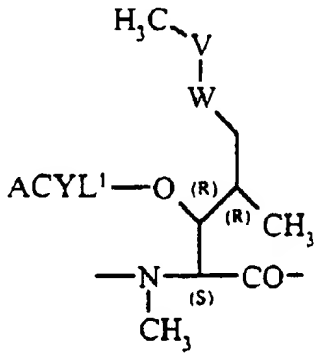
provided that, when R_4 and Z_4 are MeLeu, then R_5 and Z_5 are MeVal or methylleucine, or R_1 and Z_1 are 8'-hydroxy-MeBmt; or

viii) the radicals R_1, R_2, and R_4 to R_{11}, and Z_1, Z_2, and Z_4 to Z_{11} define a cyclosporin in which the 3' carbon of the residue at the 1-position or the β carbon of the residue at the 2-position is substituted by O-acyl or oxo; and

Z_1 and R_1 are radicals such that there is, at the 1-position, a residue of formula



(IIId)

in which -V-W- is CH_2-CH_2 or trans CH=CH and $ACYL^1$ is an acyl group; and

Z_2 and R_2 are radicals such that there is, at the 2-position, an amino acid α-aminobutyric acid, valine, threonine, norvaline, or a β-O-acylated α-amino acid; and

Z_5 and R_5 are radicals such that there is, at the 5-position, an amino acid valine or norvaline when there is simultaneously an amino acid norvaline at the 2-position; and

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Z_8 and R_8 are radicals such that there is, at the 8-position, an amino acid D-alanine or a β-O-acylated or β-hydroxylated α-amino acid having the D configuration; and

the radicals at the 4-, 6-, 7-, and 9- to 11-positions are defined as for cyclosporin A; and

one or more hydroxyl groups and optionally one or more non-methylated nitrogen atoms at the α position and optionally any other deprotonatable acidic group present in said formula (II) are optionally deprotonated or in the protected form.

5. The process according to claim 1, in which said hexamethyldisilazane metal salt is a hexamethyldisilazane alkali metal salt.

6. A process according to claim 5, in which said hexamethyldisilazane metal salt is chosen from the hexamethyldisilazane lithium salt, the hexamethyldisilazane sodium salt, and the hexamethyldisilazane potassium salt.

7. The process according to claim 6, in which said hexamethyldisilazane metal salt is used in an amount ranging from 20 to 30 molar equivalents.

8. The process according to claim 2, in which, when the treatment of the cyclosporin is carried out in the presence of a metal halide, said metal halide is chosen from lithium chloride, caesium chloride, caesium fluoride, cuprous chloride, and mercuric chloride.

9. The process according to claim 8, in which, when said metal halide is caesium chloride or lithium chloride, it is used in an amount ranging from 2 to 8 molar equivalents.

10. The process according to claim 9, in which the treatment of the cyclosporin is carried out in an aliphatic or cyclic ether, an aromatic hydrocarbon, or a

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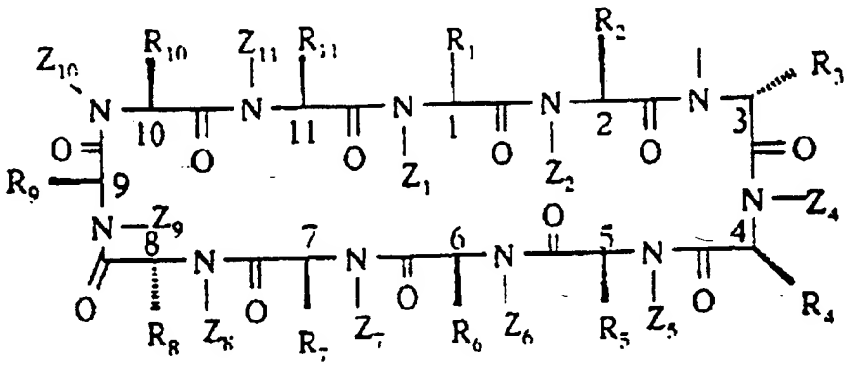
mixture of these solvents.

11. The process according to claim 10, in which the treatment of the cyclosporin is carried out at a temperature ranging from -40°C to 0°C.

12. The process according to claim 11, in which the treatment of the cyclosporin is carried out with a ratio (weight/weight) of cyclosporin involved with respect to the total weight of the solution which is less than or equal to 10%.

13. A process for preparing a cyclosporin derivative substituted at the 3-position, said process comprising preparing a polyanion by treating a cyclosporin with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide, adding an electrophilic agent to said treated cyclosporin, and, optionally converting the product of said addition to a salt, wherein the hydroxyl radicals, if any, present on the cyclosporin which may possibly interfere with the reaction are protected before said treatment and then the protective radicals are removed, after said treatment.

14. The process according to claim 13, in which at least one obtained cyclosporin derivative substituted at the 3-position has the formula:



(IV)

in which:

1) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in i) and R_3 is a radical -S-Alk-R° in which:

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Alk is an alkylene radical comprising from 2 to 6 straight- or branched-chain carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms; and

R° is

a carboxyl or alkyloxycarbonyl radical; or

an $-NG_1G_2$ radical in which G_1 and G_2, which are identical or different, are each

a hydrogen atom; or

a phenyl, cycloalkyl (C_{3-6}), alkenyl (C_{2-4}), or alkyl radical, each of which is optionally substituted by a halogen atom, an alkyloxy, alkyloxycarbonyl, amino, alkylamino, or dialkylamino radical; or

a benzyl radical or a saturated or unsaturated heterocyclyl radical comprising 5 or 6 ring members and from 1 to 3 heteroatoms; or

G_1 and G_2 form, with the nitrogen atom to which they are attached, a saturated or unsaturated heterocycle comprising from 4 to 6 ring members which can comprise another heteroatom chosen from nitrogen, oxygen, and sulphur and which is optionally substituted by alkyl, phenyl, or benzyl; or

a radical of formula:

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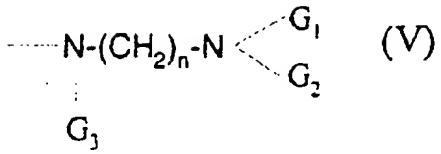


(V)

in which G_1 and G_2 are defined as above, G_3 is a hydrogen atom or an alkyl radical, and n is an integer from 2 to 4, the alkyl portions or radicals defined above are straight or branched and comprise from 1 to 4 carbon atoms; or

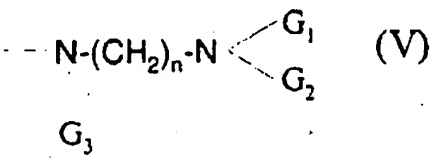
2) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in ii) and R_3 is -S-CH_3 or a radical -S-Alk-R° in which:

Alk is an alkylene radical comprising from 2 to 6 straight- or branched-chain carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms; and

R° is

a hydroxyl, carboxyl, or alkyloxycarbonyl radical; or

an -NG_1G_2 radical or a radical of formula:



(V)

as defined above; or

3) the R_1 to R_{11} and Z_1 to Z_{11} radicals are as defined in claim 4 in iii) and R_3 a radical of structure -S-Alk-R° in which:

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Alk is an alkylene radical comprising from 2 to 6 straight- or branched-chain carbon atoms or a cycloalkylene radical comprising from 3 to 6 carbon atoms; and

R° is

a hydrogen atom or a hydroxyl, carboxyl, or alkyloxycarbonyl radical; or

an $-NG_1G_2$ radical in which G_1 and G_2, which are identical or different, are each

a hydrogen atom; or

a phenyl, cycloalkyl (C_{3-6}), or alkyl radical, each of which is optionally substituted by a halogen atom, or an alkyloxy, alkyloxycarbonyl, amino, alkylamino, or dialkylamino radical; or

a benzyl radical or a saturated or unsaturated heterocyclyl radical comprising 5 or 6 ring members and from 1 to 3 heteroatoms; or

G_1 and G_2 form, with the nitrogen atom to which they are attached, a 5- or 6-membered heterocycle which can comprise another heteroatom chosen from nitrogen, oxygen, and sulphur and which is optionally substituted by alkyl; or

a radical of formula:

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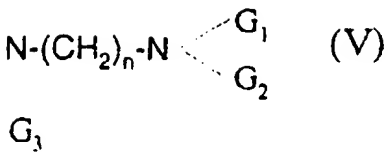

(V)

as defined above; or

4) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in iv) and R_3 is a radical chosen from:

straight or branched alkyl (C_{2-6}), alkenyl, or alkynyl, each of which is optionally substituted by a hydroxyl, amino, C_{1-4} alkylamino, C_{1-3} dialkylamino, alkyloxy, or acyloxy group;

$COOG_4$ or $CONHG_4$, in which G_4 is a straight or branched alkyl comprising from 1 to 4 carbon atoms;

$-Y-G_5$, in which Y is S or O, and G_5 is a straight or branched C_1 to C_4 alkyl, a straight or branched alkenyl, or a straight or branched alkynyl, and in which, if Y is S, G_5 can also be an aryl or a heteroaryl;

a halo or cyano group; and

CHG_6G_7, in which G_6 is a hydrogen atom or a methyl, ethyl, or phenyl group and G_7 is a hydrogen atom or a hydroxyl, halo, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, acyloxy, *t*-butoxycarbonylaminoethoxyacetyloxy, or alkyloxycarbonyl group; or

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5) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in v) and R_3 is a radical such that there is, at the 3-position, an α-(methylmercapto)sarcosyl or N-methyl-D-alanyl residue; or

6) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in vi) and R_3 is a C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, mercaptoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{2-5}alkoxycarbonylamino(C_{1-4}alkyl), nitroC_{1-6}alkyl, cyanoC_{1-5}alkyl, C_{1-6}alkoxy(C_{1-6}alkyl), C_{1-6}alkylthio-(C_{1-6}alkyl), C_{2-7}alkanoyloxy(C_{1-6}alkyl), C_{2-7}diazoalkanoyloxy(C_{1-6}alkyl), carboxy(C_{1-6}alkyl), C_{2-7}alkoxycarbonyl(C_{1-6}alkyl), aminocarbonyl(C_{1-4}alkyl), aminocarbonyloxy(C_{1-4}alkyl), amino(C_{1-4}alkanoyloxy)(C_{1-4}alkyl), amino(C_{2-9}alkoxycarbonyl)(C_{1-4}alkyl), C_{2-7}alkylcarbonyl, C_{2-7}alkoxycarbonyl, C_{1-6}alkylthio, hydroxyC_{1-6}alkylthio, C_{1-6}alkoxy(C_{1-6}alkylthio), C_{2-11}alkanoyloxy(C_{2-4}alkylthio), C_{2-11}alkanoyloxy(C_{2-4}alkylsulphinyl), C_{2-11}alkanoyloxy(C_{2-4}alkylsulphonyl), aminocarbonyloxy(C_{2-4}alkylthio), C_{2-11}aminoalkanoyloxy(C_{2-4}alkylthio), aminocarbonyloxy(C_{2-4}alkylsulphinyl), aminocarbonyloxy(C_{2-4}alkylsulphonyl), aminoalkanoyloxy(C_{2-4}alkylsulphinyl), aminoalkanoyloxy(C_{2-4}alkylsulphonyl), aminocarbonyl, C_{3-6}alkenyl, C_{3-6}alkynyl, haloC_{3-6}alkenyl, haloC_{3-6}alkynyl, hydroxyC_{3-6}alkenyl, aryl(C_{1-6}alkyl), hydroxylated aryl(C_{1-6}alkyl), aryl(C_{3-6}alkenyl), aryl(C_{3-6}alkynyl), hydroxylated aryl(C_{3-6}alkenyl), hydroxylated aryl(C_{3-6}alkynyl), arylthio, heteroarylthio, aryl(C_{2-5}alkoxycarbonylamino)(C_{1-4}alkyl), halo, or cyano radical, or a radical of formula Q-(CH_2-CH_2-O)$_n$-CO-O-CH_2-, in which n is 1, 2, or 3 and Q is amino; or

7) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in vii) and R_3 is a radical such that there is, at the 3-position, an amino acid D-MeAla; or

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8) the radicals R_1 to R_{11} and Z_1 to Z_{11} are as defined in claim 4 in viii) and R_3 is a radical such that there is, at the 3-position, an α-amino acid which is N-methylated at the α position and which has the D configuration.

15. A method for preventing or treating a retrovirus infection or an associated syndrome, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 1), 2), 3), 4), or 7).

16. The method of claim 15, in which the retrovirus infection is AIDS (acquired immunodeficiency syndrome).

17. A method for treating a chronic inflammatory disease or an autoimmune disease, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 5).

18. A method for preventing or treating an autoimmune disease or preventing rejection of a transplanted organ, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 6) or 8).

19. A method for treating inflammation, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 6) or 8).

20. The method of claim 19, in which the inflammation is an arthritis or a rheumatic disease.

21. A method for treating schistosomiasis, filariasis, leishmaniasis, coccidioidomycosis, or malaria, comprising administering to a mammal in need or desire thereof an effective amount of a cyclosporin derivative as defined in claim 14 in 6) or 8).

22. The process according to claim 1, wherein when R_i in formula (IIIb) is propenyl, the double bond exhibits a trans configuration.

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23. The process according to claim 13, wherein said cyclosporin derivative substituted at the 3-position is chosen from:

[(R)-2-aminoethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-methylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-ethylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-isopropylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-*t*-butylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-phenylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-benzylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-methyl-N-ethylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-methyl-N-allylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N-methyl-N-phenylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N,N-diisopropylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(N,N-diallylamino)ethylthio-Sar]^3-cyclosporin A;

[(R)-3-aminopropylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-methylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-ethylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-isopropylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-*t*-butylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-phenylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-benzylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-methyl-N-ethylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-methyl-N-isopropylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-methyl-N-*t*-butylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-methyl-N-allylamino)propylthio-Sar]^3-cyclosporin A;

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[(R)-3-(N-methyl-N-phenylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N-methyl-N-benzylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N,N-diethylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N,N-diisopropylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(N,N-diallylamino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(1-piperidyl)propylthio-Sar]^3-cyclosporin A;

[(R)-4-aminobutylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-ethylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-isopropylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-*t*-butylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-phenylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-benzylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methyl-N-ethylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methyl-N-isopropylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methyl-N-*t*-butylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methyl-N-allylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methyl-N-phenylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N-methyl-N-benzylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N,N-dimethylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N,N-diethylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N,N-diisopropylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(N,N-diallylamino)butylthio-Sar]^3-cyclosporin A;

[(R)-4-(1-piperidyl)butylthio-Sar]^3-cyclosporin A;

[(R)-2-amino-2-methylpropylthio-Sar]^3-cyclosporin A;

[(R)-2-(N,N-dimethylamino)-2-methylpropylthio-Sar]^3-cyclosporin A;

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[(R)-2-(N,N-diethylamino)-2-methylpropylthio-Sar]^3-cyclosporin A;

[(R)-2-(1-piperidyl-2-methylpropylthio-Sar]^3-cyclosporin A;

[(R)-3-amino-3-methylbutylthio-Sar]^3-cyclosporin A;

[(R)-3-(N,N-dimethylamino)-3-methylbutylthio-Sar]^3-cyclosporin A;

[(R)-3-(N,N-diethylamino)-3-methylbutylthio-Sar]^3-cyclosporin A;

[(R)-3-(1-piperidyl)-3-methylbutylthio-Sar]^3-cyclosporin A;

[(R)-2-(1-morpholino)ethylthio-Sar]^3-cyclosporin A;

[(R)-2-(1-azetidino)ethylthio-Sar]^3-cyclosporin A;

{(R)-2-[1-(4-methylpiperazino)]ethylthio-Sar}^{3}-cyclosporin A;

{(R)-2-[1-(4-phenylpiperazino)]ethylthio-Sar}^{3}-cyclosporin A;

{(R)-2-[1-(4-benzylpiperazino)]ethylthio-Sar}^{3}-cyclosporin A;

{(R)-2-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}^{3}-cyclosporin A;

{(R)-2-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}^{3}-cyclosporin A;

[(R)-3-(1-morpholino)propylthio-Sar]^3-cyclosporin A;

[(R)-3-(1-azetidino)propylthio-Sar]^3-cyclosporin A;

{(R)-3-[1-(4-methylpiperazino)]propylthio-Sar}^{3}-cyclosporin A;

{(R)-3-[1-(4-phenylpiperazino)]propylthio-Sar}^{3}-cyclosporin A;

{(R)-3-[1-(4-benzylpiperazino)]propylthio-Sar}^{3}-cyclosporin A;

{(R)-3-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}^{3}-cyclosporin A;

{(R)-3-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}^{3}-cyclosporin A;

[(R)-2-aminoethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-ethylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-isopropylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-*t*-butylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-phenylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

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[(R)-2-(N-benzylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methyl-N-ethylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methyl-N-isopropylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methyl-N-tert-butylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methyl-N-allylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methyl-N-phenylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N-methyl-N-benzylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N,N-diethylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N,N-diisopropylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N,N-diallylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(1-piperidyl)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-aminopropylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-ethylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-isopropylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-tert-butylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-phenylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-benzylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methyl-N-ethylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methyl-N-isopropylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methyl-N-*t*-butylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methyl-N-allylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methyl-N-phenylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N-methyl-N-benzylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N,N-dimethylamino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N,N-diethylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

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[(R)-3-(N,N-diisopropylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N,N-diallylamino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(1-piperidyl)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-aminobutylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-ethylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-isopropylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-*t*-butylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-phenylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-benzylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methyl-N-ethylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methyl-N-isopropylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methyl-N-*t*-butylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methyl-N-allylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methyl-N-phenylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N-methyl-N-benzylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N,N-dimethylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N,N-diethylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N,N-diisopropylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(N,N-diallylamino)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-4-(1-piperidyl)butylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-amino-2-methylpropylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N,N-dimethylamino)-2-methylpropylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(N,N-diethylamino)-2-methylpropylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(1-piperidyl)-2-methylpropylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-amino-3-methylbutylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

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[(R)-3-(N,N-dimethylamino)-3-methylbutylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(N,N-diethylamino)-3-methylbutylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(1-piperidyl)-3-methylbutylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(1-morpholino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-2-(1-azetidino)ethylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-2-[1-(4-methylpiperazino)]ethylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-2-[1-(4-phenylpiperazino)]ethylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-2-[1-(4-benzylpiperazino)]ethylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-2-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-2-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]ethylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(1-morpholino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

[(R)-3-(1-azetidino)propylthio-Sar]^3-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-3-[1-(4-methylpiperazino)]propylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-3-[1-(4-phenylpiperazino)]propylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-3-[1-(4-benzylpiperazino)]propylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A;

{(R)-3-[1-(4-methyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A; and

{(R)-3-[1-(4-phenyl-1,2,3,6-tetrahydropyridyl)]propylthio-Sar}^{3}-[4'-hydroxy-MeLeu]^4-cyclosporin A.

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